# The distant organ effects of acute kidney injury

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**Despite the availability of renal replacement therapy, acute kidney injury (AKI) is associated with high mortality and morbidity. In humans, it is difficult to determine whether AKI is a cause or consequence of excess morbidity. In animal models, however, it is increasingly clear that AKI induces distant organ dysfunction. Identified pathways include inflammatory cascades, apoptosis, the induction of remote oxidative stress, and differential molecular expression. Specifically, growing evidence implicates renal injury as an instigator and multiplier of pulmonary, cardiac, hepatic, and neurologic dysfunction. Accurate identification of these pathways will be critical in developing targeted therapies to improve outcomes in AKI. The purpose of this review is to summarize both clinical and preclinical studies of AKI and its role in distant organ injury.**

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Acute kidney injury (AKI) is common, increasing in incidence, and associated with excess morbidity and mortality in the critically ill patient.[1–3] Despite widespread availability of renal replacement therapy, a hospitalized patient who develops AKI faces a mortality risk as high as 40–60%.[2,4,5] Much of this mortality risk is thought to stem from extrarenal complications or the distant organ effects of AKI.

The mechanisms by which AKI increases the risk of adverse outcomes are incompletely understood. In humans, determining causality is difficult: does AKI itself cause excess morbidity and mortality, or is it simply a by-product of the underlying severity of illness? Thus, animal models are vital in order to clarify physiological mechanisms and test new therapeutics. In these animal models, the causal distinction is clearer: injuring (or removing) the kidneys results in deleterious systemic effects and distant organ dysfunction. Recent experimental models have elucidated some potential mechanisms of injury, including dysfunctional inflammatory cascades, oxidative stress, activation of proapoptotic pathways, differential molecular expression, and leukocyte trafficking (Figure 1).

The bilateral renal ischemia–reperfusion injury (IRI) model, which causes both decreased renal function and ischemic organ injury in experimental animals, has been most commonly used to study distant organ effects of AKI. This model is clinically relevant given that a significant portion of in-hospital AKI is thought to be ischemic in nature.[6] The bilateral nephrectomy (BNx) model, on the other hand, may represent the isolated impact of absent renal function. Many experimental studies use both models to compare the effects of kidney IRI and lack of kidney function with the lack of kidney function only. Initially applied to kidney-lung interaction (Table 1), and more recently used in kidney–heart, kidney–liver, and kidney–brain studies (Table 2), these experimental models have yielded important insights in the complex organ cross-talk that occurs after AKI.

Why is the elucidation of pathways involved in organ cross-talk in AKI important? Mortality in patients with AKI is high, and therapy is limited.[1,3,7] Increased delivery of renal replacement therapy does not appear to improve outcomes.[8] Identification of the mechanisms by which AKI affects distant organ function is critical to the development and refinement of therapies to prevent or attenuate AKI-associated morbidity and mortality. In this review, we summarize the growing

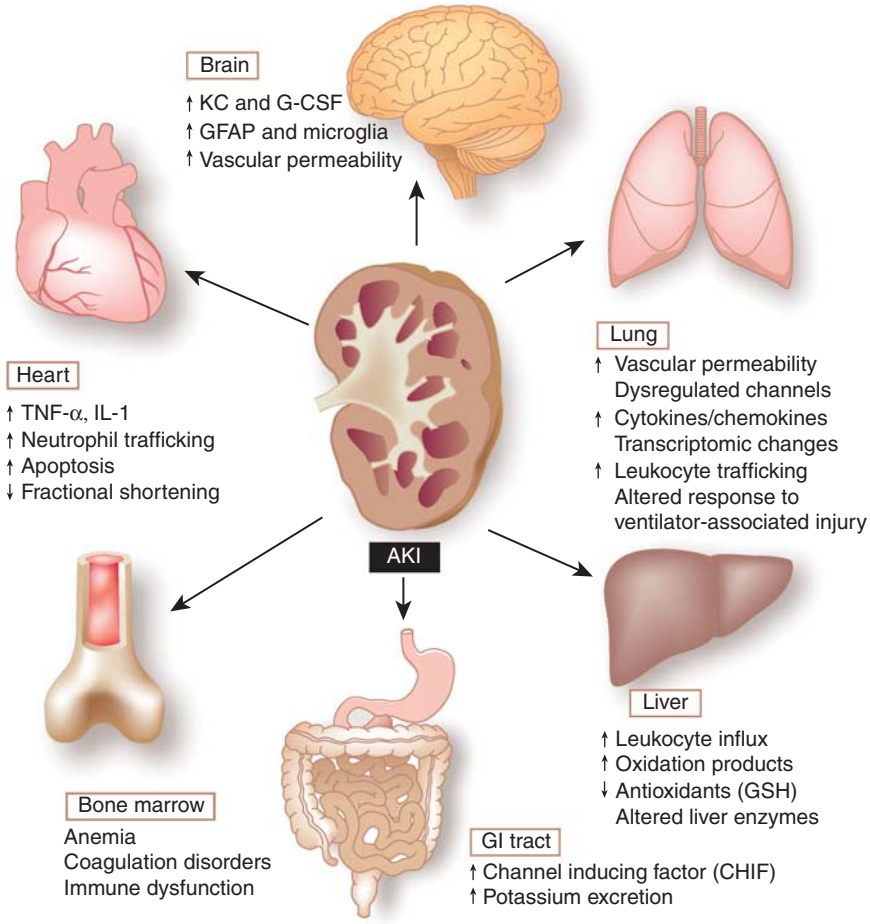


**Figure 1 | Distant organ consequences of AKI**. AKI, acute kidney injury; G-CSF, granulocyte colony-stimulating factor; GFAP, glial fibrillary acidic protein; GI, gastrointestinal; GSH, glutathione; IL, interleukin; KC, keratinocyte-derived chemokine; TNF, tumor necrosis factor.
Note: Used with permission from Scheel *et al.*[64]

**Table 1 | Experimental studies on the pulmonary effects of AKI**

| AKI model | Species | Reference | Findings |
|---|---|---|---|
| IRI | Rat | Kramer *et al.*[22] | AKI caused increased pulmonary vascular permeability; macrophage inhibition attenuated this response. |
| IRI and BNx | Rat | Rabb *et al.*[25] | AKI in both models caused downregulation of lung ENaC, Na,K-ATPase, and aquaporin-5; unilateral IRI did not. |
| IRI | Mouse | Deng *et al.*[26] | ALI occurred within 4 h after AKI; treatment with an anti-inflammatory cytokine (α-MSH) decreased lung injury. |
| IRI | Mouse | Nath *et al.*[24] | ALI and mortality after AKI was heightened in the presence of baseline comorbid condition (sickle-cell disease). |
| IRI, BNx and sepsis | Rat | Kim *et al.*[29] | ALI occurred in all AKI models; ALI after BNx had less cellular infiltration and different inflammatory mediator expression as compared with ALI from sepsis. |
| IRI and BNx | Mouse | Zarbock *et al.*[33] | Acid-induced ALI was attenuated in the presence of AKI via either model; impaired pulmonary recruitment of uremic neutrophils mediated this response. |
| IRI and BNx | Mouse | Hoke *et al.*[23] | ALI occurred after AKI in both models; serum cytokine profiles after AKI varied by AKI model; IL-10 attenuated lung injury after bilateral nephrectomy. |
| IRI and BNx | Mouse | Hassoun *et al.*[30] | ALI occurred after IRI but not BNx; transcriptional changes in the lung after IRI were distinct from those after BNx. |
| IRI | Mouse | Tracz *et al.*[28] | IL-6 levels were significantly elevated after IRI in heme oxygenase-1 ($HO\text{-}1^{-/-}$) knockout mice (which are highly sensitive to IRI); IL-6 antibodies decreased their exaggerated renal and mortality response to IRI. |
| IRI and BNx | Mouse | Klein *et al.*[27] | ALI after AKI by either method was attenuated in IL-6-deficient mice and in wild-type mice treated with anti-IL-6 antibody. |
| IRI | Mouse | Hassoun *et al.*[31] | Lung activation of 66 apoptosis-related genes occurred after AKI; correlated with TUNEL staining and active caspase-3 activity, indicating pulmonary epithelial apoptosis. |
| IRI | Mouse | Awad *et al.*[32] | Used flow cytometry to follow *in vivo* neutrophil trafficking, showed an increase in marginated neutrophils but not interstitial neutrophils in the lung after kidney ischemia. |

Abbreviations: AKI, acute kidney injury; ALI, acute lung injury; BNx, bilateral nephrectomy; ENaC, epithelial sodium channel; IL, interleukin; IRI, ischemia–reperfusion injury; α-MSH, α-melanocyte-stimulating hormone; TUNEL, terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling.

**Table 2 | Experimental studies on heart, liver, and brain effects of AKI**

| Organ | Species | Reference | Findings |
|---|---|---|---|
| Heart | Mouse | Kelly[46] | IRI but not BNx led to cardiac apoptosis and increased cardiac cytokines; blocking TNF-α reduced cardiac apoptosis. |
| Heart | Mouse | Nath *et al.*[24] | Compared with wild-type mice, cardiac vascular congestion was significantly worse after IRI in sickle-cell mice. |
| Liver | Mouse | Miyazawa *et al.*[49] | Increased hepatic accumulation of neutrophils and intermediate T cells were seen after unilateral IRI. |
| Liver | Mouse | Serteser *et al.*[52] | Hepatic effects of IRI, including elevated TNF-α, MPO activity, and decreased antioxidant activity, were seen after only 30 min of renal ischemia and 1 h reperfusion. |
| Liver | Rat | Golab *et al.*[50] | IRI and BNx led to early leukocyte infiltration and congestion in the liver; increased oxidative stress in the liver and elevated hepatic levels of TNF-α were also seen. |
| Liver | Mouse | Park *et al.*[51] | IRI and BNx led to acute hepatic dysfunction, peri-portal neutrophil infiltration; blocking TNF-α, IL-17A, or IL-6 protected against AKI-induced hepatic injury. |
| Brain | Rat | Adachi *et al.*[62] | Dopamine turnover was reduced in the striatum, mesencephalon, and hypothalamus after IRI. |
| Brain | Mouse | Liu *et al.*[63] | IRI led to disruption in the blood–brain barrier, increased neuronal pyknosis and microgliosis in the brain, and functional impairment in locomotor activity. |

Abbreviations: AKI, acute kidney injury; BNx, bilateral nephrectomy; IL, interleukin; IRI, ischemia–reperfusion injury; MPO, myeloperoxidase; TNF, tumor necrosis factor.

evidence of the causal and modulatory role of AKI in dysfunction of the lung, heart, liver, and brain.

## KIDNEY–LUNG INTERACTIONS: CLINICAL STUDIES

Respiratory complications are frequently associated with AKI. In a study of AKI after radiocontrast administration, 78% of patients not previously ventilated developed subsequent respiratory failure.[9] Similarly, AKI is a common occurrence in mechanically ventilated patients. In the first Acute Respiratory Distress Syndrome (ARDS) Network trial, 24% of patients with ARDS developed AKI within 4 days of study enrollment.[10–12] Mortality is increased in AKI patients requiring mechanical ventilation,[13–15] as well as ventilated patients developing AKI.[12]

Clinical studies suggest that the association between AKI and respiratory failure is not solely due to shared antecedent comorbidities: AKI itself may increase the risk of severe extrarenal morbidity.[9] In a matched pairs cohort design, patients developing AKI after radiocontrast administration were matched to patients who did not develop AKI after a similar contrast study. Even after adjustment for pre-existing comorbid conditions, the development of AKI was associated with a greater than fivefold increase in mortality risk. Patients with AKI had subsequent hospital courses marked by excess sepsis, delirium, and respiratory failure.

Inflammatory cytokines are potential mediators of the distant effects of AKI. Increases in inflammatory cytokines interleukin (IL)-6 and/or IL-8 preceded rises in serum creatinine in cohorts of patients with sepsis,[16] acute lung injury,[12] after cardiopulmonary bypass,[17,18] and in kidney transplant recipients with transplant-related ischemic injury.[19] High levels of IL-6 were associated with prolonged weaning times from the ventilator[17] and mortality in patients with AKI and acute lung injury.[20,21] Furthermore, unique patterns of cytokines were associated with death and the development of AKI in patients with acute lung injury, suggesting that AKI induces a distinct inflammatory footprint not solely reflective of the underlying severity of illness.[12]

## KIDNEY–LUNG INTERACTIONS: ANIMAL MODELS

### Increased vascular permeability

Building on the observed association between AKI and lung injury in humans, early work in animal models demonstrated that primary renal injury could lead to secondary lung injury.[22] In a rat model of bilateral renal IRI, there was increased lung vascular permeability at 24 and 48 h post ischemia, quantified by extravasation of labeled albumin outside the vascular space. Histological examination was consistent with defects in vascular permeability, with interstitial edema, occasional areas of alveolar hemorrhage, and red blood cell sludging.

Subsequent studies using a mouse model of sham surgery, unilateral IRI, bilateral IRI, and BNx demonstrated abnormal lung histology in animals undergoing BNx or bilateral renal IRI, but not unilateral IRI or sham surgery.[23] Furthermore, all experimental animals lost weight, suggesting that the pathological changes were not solely secondary to total body fluid accumulation.[22,23] In addition, AKI-induced lung injury was much worse in the presence of a comorbidity, sickle-cell disease, supporting the concept of the modulatory effect of AKI on pre-existing conditions.[9,24]

### Dysregulated channels

Postulating that the observed pulmonary edema after AKI was secondary to poor alveolar salt and water clearance, lung tissue was examined for transporters in a similar four-way rat model.[25] There was significantly decreased lung mRNA expression of epithelial sodium channel and aquaporin-5, with a concomitant decrease in aquaporin-5 protein. These results were consistent in models of BNx and bilateral renal IRI, but not unilateral IRI or sham surgery, providing evidence that differential protein expression is mediated by systemic effects of AKI and not just via by-products of ischemia.

### Increased cytokines and chemokines

Animal models support the role of inflammatory cytokines as systemic mediators of kidney–lung cross-talk. There was

significant attenuation of lung injury in a bilateral renal IRI rat model using CNI-1493, an inhibitor of macrophage activation (via inhibition of IL-1, tumor necrosis factor (TNF), and IL-6, but not of anti-inflammatory cytokines IL-10 and transforming growth factor-β), independent of an effect on AKI.[22] In another study, both renal and lung injury were decreased by pretreating mice undergoing bilateral IRI with α-melanocyte-stimulating hormone, which has a broad array of anti-inflammatory effects.[26]

The balance of proinflammatory and anti-inflammatory cytokines may be important in modulating AKI-induced lung injury. Wild-type mice treated with BNx or bilateral IRI had increased myeloperoxidase (MPO) activity, keratinocyte-derived chemokine (KC; the murine equivalent of IL-8, a neutrophil chemokine), and macrophage inflammatory protein-2 (a neutrophil chemoattractant) expression.[23,27] Administration of the anti-inflammatory cytokine IL-10 attenuated neutrophil accumulation, with a reduction in pulmonary MPO and pulmonary macrophage inflammatory protein-2.[23] Reduction in the proinflammatory cytokine IL-6 achieved similar results. IL-6-deficient mice had reduced MPO activity and KC expression after AKI, as did mice treated with an IL-6 antibody.[27] Conversely, administration of exogenous IL-6 resulted in increased pulmonary MPO activity.[27]

Additional evidence for the importance of IL-6 signaling pathways was provided in experiments involving heme oxygenase-1 (HO-1), an enzyme involved in the degradation of heme.[28] The upregulation of HO-1 in ischemic kidney is thought to be an adaptive response, as knockout HO-1 mice demonstrate a significantly reduced glomerular filtration rate after renal ischemia. After bilateral renal IRI, serum, kidney, lung, and heart IL-6 and IL-6-dependent signaling were significantly increased in HO-1 knockout mice compared with wild type. In addition, an IL-6 antibody administered before ischemia to HO-1 knockout mice significantly attenuated AKI and decreased mortality.

### Distinct inflammatory responses

The inflammatory mechanisms by which secondary lung injury occurs after renal injury are distinct from those seen in sepsis-induced lung injury.[29] Comparing cytokine induction in the lungs of rats with sepsis and BNx uncovered different patterns of inflammatory mediator and heat-shock protein expression. Although lung injury and pulmonary vascular alterations were similar in the two models, rats with BNx-induced lung injury had significantly less cellular infiltration and a marked increase in the proinflammatory chemokine CINC2. Rats with sepsis-induced lung injury, on the other hand, had evidence of TNF-α induction.

Unique systemic inflammatory patterns have also been observed with different mechanisms of AKI.[23] Comparing mice undergoing sham surgery, unilateral ischemia, bilateral ischemia, and BNx, it was found that there were varied increases in serum cytokines by mechanism of injury. Relative to sham surgery, ischemic injury produced increases in KC and granulocyte macrophage colony-stimulating factor, BNx resulted in increased IL-10 and granulocyte colony-stimulating factor, and both methods of AKI increased IL-6, IL-1β, and IL-12. In contrast, unilateral ischemia produced increases in KC only, presumably via increased production in the ischemic kidney, thus demonstrating the importance of normal kidney function in the regulation of cytokines.

### Transcriptomic changes

Distinct inflammatory signatures of bilateral IRI and BNx have also been demonstrated via global gene expression profiling of the lung transcriptome.[30] An analysis of pulmonary RNA expression revealed overlapping but distinct patterns of candidate gene upregulation and downregulation in BNx versus IRI mice. Gene ontology analysis showed time-dependent activation of both proinflammatory and proapoptotic processes, with upregulation of immune and inflammation genes early after AKI and later activation of ubiquitin- and apoptosis-related genes.

The role of proapoptotic processes in AKI-induced acute lung injury was supported in work combining genomic-based models with interventional experiments.[31] In mouse models of bilateral IRI, activation of 66 apoptosis-related genes was identified through a lung candidate gene discovery approach. These findings were correlated in functional experiments by increased terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling (TUNEL) and increased caspase-3 activity colocalizing with CD34, indicating increased endothelial apoptosis. In addition, pretreatment with the caspase inhibitor Z-VAD-FMK reduced microvascular distortion in the lung after AKI. Finally, a TNF receptor-1-dependent pathway was implicated by increased transcription of the TNF receptor superfamily, and the absence of lung apoptosis in TNF receptor-1 knockout mice.

### Increased leukocyte trafficking

Neutrophil infiltration in the lung has been demonstrated in both BNx and bilateral IRI models of AKI.[26,27,29] Unlike the kidney, however, in which the sequential recruitment of neutrophils from vasculature to interstitium can be blocked by an adenosine 2A receptor agonist, only marginated neutrophils increased in the lung after AKI.[32]

### Altered response to lung injury

Kidney injury may elicit compensatory mechanisms that attenuate remote organ injury. In a 'two-hit' mouse model of experimental renal injury, followed by hydrochloric acid-induced lung injury, acute uremia resulted in impaired pulmonary recruitment of neutrophils following both BNx and bilateral IRI.[33] Furthermore, AKI may exhibit modulatory effects that vary with the severity of lung injury. In a model of ventilator-induced lung injury, mice with AKI had less lung injury (as quantified by extravasation of Evans Blue Dye and pulmonary neutrophil infiltration) than sham animals in high tidal volume-treated strategies, and more lung injury in low tidal volume-treated strategies.

### Lung injury: effects on the kidney

Kidney–lung cross-talk—the remote influence not only of the injured kidney on the lung but also of the injured lung on the kidney—is suggested in clinical studies, but experimental evidence is conflicting. In a rabbit model of acid-induced lung injury, TUNEL-positive renal tubular epithelial cells were seen in animals undergoing high tidal volume ventilation (an 'injurious' strategy), but not in animals undergoing low tidal volume ventilation (a 'non-injurious' strategy).[34] Examination by electron micrography demonstrated increased apoptosis and cytoplasmic bleb formation in renal tubular epithelial cells of the injurious animals. Similarly, incubation with plasma from injurious animals resulted in increased apoptosis in rabbit renal proximal tubular cells *in vitro*. Correlation in human studies was performed by measuring plasma soluble Fas ligand in patients randomized to a high or low tidal volume strategy in the ARDS Network clinical trial.[10] Patients in the high tidal volume strategy had significant higher plasma soluble Fas ligand levels, and changes in serum creatinine were significantly correlated with changes in soluble Fas ligand. In contrast, in a canine model of acid-induced lung injury where blood pressure and fluids could be optimally managed, there was no change in renal parameters—including renal blood flow, urine output, serum creatinine, albuminuria, and kidney histology when compared with sham-operated animals.[35]

## KIDNEY–HEART INTERACTIONS: CLINICAL STUDIES

Cardiorenal syndromes type 1 and 3, where acute dysfunction in the heart induces decreased kidney function and vice versa, respectively, are increasingly recognized but poorly understood.[36] Approximately 20–30% of patients hospitalized with congestive heart failure (CHF) will reach the threshold for Stage 1 AKI defined by the AKI Network,[37] and even small amounts of renal injury are associated with increased mortality in these patients.[38] Among patients with established AKI, 'cardiac failure' has been reported as a common cause of death.[39]

Acute cardiac decompensation is thought to affect the kidney via hemodynamic mechanisms, as well as humoral and immune-mediated pathways.[36] Less established is the mechanism of type 3 cardiorenal syndrome, where AKI causes an acute cardiac disorder, such as CHF or arrhythmias. AKI-induced salt and water retention likely increases preload; however, it is also speculated that AKI induces endothelial cell activation, cytokine secretion, and proapoptotic cascades, resulting in myocardial damage via neutrophil infiltration and myocyte apoptosis and necrosis.[40]

Increased production and impaired clearance of inflammatory cytokines may adversely affect myocardial function and viability. Elevated levels of TNF and IL-6 are associated with worsening New York Heart Association functional status,[41] mortality in CHF,[42] and the development of CHF.[43] Increases in modulators of apoptotic pathway are correlated with the severity of CHF.[44,45]

## KIDNEY–HEART INTERACTIONS: ANIMAL MODELS

There are limited experimental studies addressing kidney–heart interactions. In transgenic sickle mice, bilateral renal IRI resulted in marked cardiac vascular congestion and increased serum amyloid P-component (the murine equivalent of c-reactive protein).[24] In wild-type mice, renal ischemia increased cytokine expression in the heart, caused apoptosis of myocytes, and impaired cardiac function.[46] Post renal ischemia, cardiac levels of TNF-α, IL-1, and intracellular adhesion molecule-1 were elevated. Cardiac neutrophil infiltration was suggested by increased MPO activity. Increased apoptosis was detected by TUNEL staining after bilateral renal IRI but not after BNx. Administration of TNF-α antibody decreased cardiac TUNEL staining, suggesting TNF-α-mediated apoptosis as a mechanism for AKI-induced cardiac dysfunction. Echocardiography in mice with AKI showed evidence of left ventricular dilation, increased relaxation time, and decreased fractional shortening.

## KIDNEY–LIVER INTERACTIONS: CLINICAL STUDIES

Type 1 hepatorenal syndrome, a deadly complication of end-stage liver disease, is a well-described cause of AKI.[47] Here, altered intra-hepatic hemodynamics are thought to cause decreased glomerular filtration rate in an intrinsically normal kidney.[48] In contrast, there is limited clinical data on the effect of AKI on liver function. Liver dysfunction commonly coexists with AKI, particularly in the intensive care unit setting, and its presence independently increases the mortality risk.[14]

## KIDNEY–LIVER INTERACTIONS: ANIMAL MODELS

### Altered liver enzymes, increased leukocyte influx

Many of the same processes involved in kidney–lung and kidney–heart interactions have been observed in the liver: increased neutrophil infiltration, vascular congestion, and vascular permeability after AKI.[49–51] In addition, both experimental kidney ischemia and BNx led to elevated aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and bilirubin levels.[50,51]

### Increased cytokines and apoptosis

Inflammatory and apoptotic pathways are also implicated in the kidney–liver cross-talk. Following experimental AKI, hepatic TNF-α, IL-6, IL-17A, intracellular adhesion molecule-1, KC, IL-10, and monocyte chemoattractant protein-1 are increased.[50–52] Knockout mice for TNF-α, IL-17A, and IL-6 displayed reduced hepatic injury after renal ischemia, as did wild-type mice treated with antibodies to the cytokines.[51] The role of apoptosis was suggested by increased activated caspase-3 staining in hepatocytes after experimental AKI, as well as increased TUNEL positivity in the peri-portal region.[50,51]

### Increased oxidative stress and decreased antioxidants

Renal ischemia can induce hepatic oxidative stress, as evidenced by the decreased levels of superoxide dismutase

and total glutathione and increases in liver malondialdehyde.[50,52] In a rat model of bilateral renal IRI, pretreatment with a reduced form of the antioxidant glutathione resulted in a significant improvement in liver histology, as well as reduced malondialdehyde.[50]

### Altered response to hepatic injury

In contrast to experimental studies in kidney-lung interaction,[33] the presence of AKI before a 'second hit' of ischemic hepatic injury exacerbated liver injury.[51] Mice treated with BNx, bilateral renal IRI, or unilateral renal IRI all had significantly increased alanine aminotransferase, as well as increased necrosis, vascular congestion, and inflammation on histological staining. In addition, expression of IL-6, intracellular adhesion molecule-1, and monocyte chemoattractant protein-1 were much higher in mice undergoing both AKI and hepatic injury than sham animals, animals with AKI only, and animals with hepatic injury only.[51]

## KIDNEY–BRAIN INTERACTIONS: CLINICAL STUDIES

Neurological complications of AKI include central nervous system dysfunction with irritability, attention deficits, hyperreflexia, postural tremor, decreased mental status, seizures, and death. Although found in patients with advanced chronic kidney disease, adverse neurological effects including 'uremic encephalopathy' are thought to be more common and more severe in AKI.[53,54] The pathophysiology of this interaction is poorly understood. The level of azotemia does not correlate well with neurological impairment.[55] In addition, treatment with renal replacement therapy does not fully ameliorate the symptoms: sluggishness, memory impairment, and sleep disturbances may persist.[53]

The reverse process—renal changes secondary to neurological disease—is less established. AKI is common in hospitalized patients, including those with primary neurological disorders; approximately one-quarter of patients hospitalized for subarachnoid hemorrhage and acute stroke experienced AKI.[56,57] The development of in-hospital AKI is associated with significantly worse short-term[56] and long-term mortality.[57] In addition, kidney inflammation is increased in allografts from brain-dead donors.[58]

## KIDNEY–BRAIN INTERACTIONS: ANIMAL MODELS

Classical studies of canine acute uremia demonstrated significant biochemical alterations in the brain, particularly in calcium concentrations and water handling.[59–61] More recently, the role of neurotransmitters has received attention. Bilateral renal IRI resulted in decreased dopamine turnover in the striatum, mesencephalon, and hypothalamus, as well as decreased motor activity.[62] Mice undergoing renal ischemia demonstrated increased vascular permeability, alterations in the blood–brain barrier, and increased inflammation, with elevated levels of the cytokines KC and granulocyte colony-stimulating factor. Brain histology revealed increased microglial cells (brain macrophages) and pyknotic neuronal cells in the hippocampus. No increase in apoptosis was observed. Functionally, mice with AKI had poor locomotor function that correlated with the time of kidney ischemia.[63]

## CONCLUSION

AKI is a common clinical condition in the critical care setting. In humans, extrarenal organ dysfunction frequently coexists with AKI, potentiating the already high rates of AKI-associated morbidity and mortality. In animal models, a growing body of evidence suggests that AKI itself causes distant organ injury. This deleterious interaction arises, at least in part, from systemic inflammatory changes, activation of proapoptotic pathways, increases in leukocyte trafficking, and dysregulated channel expression. Accurate identification of these pathways is critical in the development and refinement of therapies for the prevention and attenuation of AKI-related morbidity.

## DISCLOSURE

The authors declared no competing interests.

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